REMARKS

Entry of this response and reconsideration of the above-referenced application is respectfully requested. Reconsideration and withdrawal of the rejections set forth in the Office Action dated May 31, 2005 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

I. Rejections under 35 U.S.C. § 102(e)

Claim 17 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Alcime *et al.* (U.S. Patent No. 5,632,772).

A. The Present Invention.

The present invention as recited in claim 17 relates to an expandable device for delivery into a blood vessel carrying blood that includes an expandable support frame having first and second end portions, a porous polymer sleeve having inner and outer surfaces, and a coating of a cell adhesion protein carried on and attached to at least one of the inner and outer surfaces of the polymer sleeve for enhancing endothelial cell growth on the polymer sleeve.

B. The Cited Reference

ALCIME ET AL. relate to an endothelial graft which is both expandable and supportive and is provided in a form suitable for use in a branched blood vessel location.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

Alcime et al. fail to teach an expandable device for delivery into a blood vessel including a coating of a cell adhesion peptide for enhancing endothelial cell growth on the polymer sleeve as presently claimed.

The Examiner contends that heparin as disclosed by Alcime et al. "induces cell in-growth and tissue regeneration" (Office action mailed May 31, 2005, page 5). In support of this position, the Examiner first points to Col. 2, lines 41-44 of Hubbell et al. (U.S. Patent No. 6,894,022), where it is stated "The examples demonstrate optimized ratios or levels of growth factor, heparin binding domain, and heparin or heparin binding peptide sequestered within the matrix that optimally induced cell in-growth and tissue regeneration." However, the patent is directed to a matrix with bound heparin to bind heparin-binding growth factors (Col. 2, lines 16-21). Hubbell et al. nowhere states that heparin induces cell in-growth and tissue regeneration as there is an optimal ratio of "growth factor, heparin binding domain, and heparin or heparin binding peptide." In fact, one skilled in the art would recognize that it is the growth factors that induce cell in-growth and tissue regeneration. Hubbell et al. even states "While delivery systems for proteins and growth factors exist and are known, there remains a need for a matrix for use in tissue repair that promotes cellular migration and tissue in-growth into the matrix through the control of growth factor presentation and release to the migrating cells and control of cellular adhesion sites. The need is particularly great for such in-growth matrices that could locally present growth factors and retain their influence and activity locally, through affinity interactions with the matrix, as occurs in nature" (Col. 1, lines 58-67, emphasis added).

Next the Examiner points to Collins et al. (U.S. Patent No. 5,434,185) for a teaching that "heparin-like substances promotes endothelial cell growth (Office action mailed Office action mailed May 31, 2005, page 5). However, the passage states "In angiogenesis and endothelial cell growth promotion, heparin-like substances complex to bFGF, the cell surface and to the extracellular matrix, thereby enhancing mitogenicity." Nowhere does Collins et al. teach that heparin-like substances are cell adhesion proteins or that the heparin-like substances enhance endothelial cell growth as presently claimed. The teaching in Collins et al. can fairly be relied upon for a teaching that the complex of heparin-like substances and bFGF, a growth factor, enhance endothelial cell growth.

In fact, as evidenced by the following articles, abstracts of which are enclosed herewith, one skilled in the art would expect heparin to inhibit cellular adhesion and cellular proliferation. At the time of filing, heparin was known to inhibit cell adhesion by blocking P-selectin mediated cell adhesion (Atalar et al., Clin. Cardiol., 24(2):159-164, 2001). Heparin was further shown to inhibit mononuclear cell adhesion by Rogers, et al. (Arterio., Thromb., and Vasc. Bio., 16:1312-1318, 1996). Yanaka, et al. (J. Neurosurg. 85(6):1102-1107, 1996) showed heparin reduced leukocyte accumulation, which is related to cellular adhesion.

Thus, heparin cannot be relied upon as a teaching of "a cell adhesion protein" "for enhancing endothelial cell growth on the polymer sleeve" as presently claimed.

As the cited reference fails to teach each of the claimed elements, withdrawal of the rejection of claim 17 under 35 U.S.C. § 102(e) over Alcime et al. is respectfully requested.

II. Rejections under 35 U.S.C. § 103(a)

Claim 18 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Alcime et al. in view of Bhatnagar (U.S. Patent No. 5,958,428).

Claim 19 stands rejected under 35 U.S.C. § 103(a) over Alcime et al. in view of Brown et al. (U.S. Patent No. 6,071,305) and further in view of Bhatnagar.

A. The Present Invention is described above.

B. The Cited Documents

Alcime et al. is described above.

Bhatnagar teach composites that include a biomaterial having compounds thereon with enhanced cell binding with respect to collagen.

Brown et al. teach a directional drug delivery stent which includes an elongated or tubular member having a cavity containing a biologically active agent.

C. Analysis

In order to establish a *prima facie* case of obviousness there must be, *inter alia*, "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." M.P.E.P. § 2143.

Furthermore, "a reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered." *Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.*, 796 F2d 443, 230 USPQ 416 (Fed. Cir. 1986).

In addition, "it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne can not use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) *citing In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). "It is impermissible ...simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps." *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991).

1. Rejection of claim 18

The Examiner relies on Alcime et al. for allegedly teaching a product recited in claim 18. Bhatnagar is relied on for allegedly disclosing use of spacer arms to facilitate binding of peptides to a substrate. The Examiner concludes it would have been obvious to provide spacers/linkers as taught by Bhatnagar in order to link the peptides to the Alcime et al. substrate, asserting that this is a well known and conventional means of attaching biomolecules to a substrate.

As noted above, Alcime et al. fail to show or suggest the expandable device recited in pending claim 17 (upon which claim 18 depends and which therefore includes all of the claim limitations of claim 17) for the same reasons set forth above.

Applicants submit it cannot be said to be obvious to modify the endothelial graft of Alcime et al. to include the synthetic peptide of Bhatnagar in order to arrive at the expandable device including a "a coating of a cell adhesion peptide carried on and attached to at least one of the inner and outer surfaces of the polymer sleeve" as presently claimed. As noted above, Alcime et al. fail to show or suggest a cell adhesion peptide carried on and attached to a polymer sleeve. Bhatnagar also fails to show or suggest this feature and instead teach synthetic compounds with enhanced cell binding attached to a porous polymer apparatus. The polymer sleeve of the present invention is a thin polymer covering the expandable support frame and provides only inner and outer surfaces for attachment of the coating of the cell adhesion peptide. One skilled in the art would have no way of knowing whether the polymer sleeve of the present invention would support the attachment of enough of a cell adhesion peptide to promote endothelialization. Further, as Bhatnagar fails to teach an expandable support, one skilled in the art would have no way of knowing that such attached coating would be sustainable during and after the expansion of the support. A major problem in expandable devices is to keep the therapeutic agent on the polymer sleeve during and after expansion.

In view of the above, withdrawal of the rejection of claim 18 under 35 U.S.C. § 103(a) over Alcime et al. in view of Bhatnagar is respectfully requested.

2. Rejection of claim 19

Alcime et al. is relied on for allegedly disclosing the invention as claimed. Brown et al. is relied on for allegedly teaching the use of therapeutic drugs such as heparin or collagen on a stent. Bhatnagar is relied on for allegedly teaching the functions of collagen and for allegedly providing synthetic peptides which are allegedly the same as applicant's peptide in SEQ ID NO:1. The Examiner concludes that, because both Alcime et al. and Brown et al. teach the use of providing a therapeutic drug such as heparin or other drugs on a stent, and Brown teaches the drug may be collagen, it would have been obvious to provide collagen as the therapeutic drug in the Alcime et al. stent with the polymer sleeve. The Examiner

further concludes that it would have been obvious to provide a synthetic peptide disclosed by Bhatnagar on the Alcime et al. stent as an alternative to collagen because it would allegedly be desirable to obtain the same therapeutic effect as collagen but without the adverse effects of collagen that are taught by Bhatnagar.

As noted above, the combination of Alcime et al. and Bhatnagar cannot be said to render the presently claimed porous polymer sleeve having a coating of a cell adhesion peptide carried on an attached to the polymer sleeve as there is no motivation to combine the references along the lines of the claimed invention. Nor does the teaching in Brown provide the missing motivation. Brown et al. teach a directional drug delivery stent which includes an elongated or tubular member having a cavity containing a biologically active agent. The biologically active agent is described therein as residing in the cavity and is for directional delivery. Nowhere does Brown make any mention of a polymer sleeve or of a peptide attached thereto. Accordingly, one skilled in the art would therefore not be motivated to combine the cited documents to arrive at the present claims.

III. Conclusion

In view of the above, applicants submit that claims 17-19 are in condition for allowance. Therefore, a Notice of Allowance is respectfully requested.

If the Examiner believes a telephone conference would expedite the prosecution of the present application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

Jacqueline F. Mahoney

Date: Nov. 30, 2005

Jacqueline F. Mahoney
Registration No. 48,390

Correspondence Address:
Customer No. 22918

About Entrez
Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI

Related Resources
Order Documents
NLM Mobile
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: J Neurosurg. 1996 Dec;85(6):1102-7. Related Articles, Links

Reduction of brain injury using heparin to inhibit leukocyte accumulation in a rat model of transient focal cerebral ischemia. I. Protective mechanism.

Yanaka K, Spellman SR, McCarthy JB, Oegema TR Jr, Low WC, Camarata PJ.

Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, USA.

Heparin has long been established as an anticoagulant. Although heparin has been demonstrated to reduce brain injury after ischemia and reperfusion, its mechanism of action remains unknown. Recent investigations reveal that it can modulate biological processes such as binding to adhesion receptors on endothelial cells and leukocytes. The authors hypothesized that heparin's protective effect is closely related to its antileukocyte adherence property. They evaluated the efficacy of sulfated polysaccharides (unfractionated heparin, low-molecular-weight heparin, heparan sulfate, chondroitin sulfate C, and dextran sulfate) on leukocyte accumulation, infarction size, and neurological outcome after transient focal cerebral ischemia in rats subjected to 1 hour of ischemia and 48 hours of reperfusion. Forty-nine animals were included in the study. The animals receiving unfractionated heparin or dextran sulfate showed a significant reduction in leukocyte accumulation, infarct size, and neurological dysfunction 48 hours after reperfusion ($p < 0.05$) when compared to untreated animals. The animals receiving unfractionated heparin also showed significantly better results than the animals receiving an equivalent anticoagulant dose of low-molecular-weight heparin. These data indicate that heparin's antileukocyte property plays a more important role than its anticoagulant ability in neuronal protection. The relative potency of the sulfated polysaccharides tested in leukocyte depletion was closely related to their degree of sulfation. Thus, in addition to demonstrating the potential efficacy of heparin as a therapeutic agent for ischemia and reperfusion injury by the prevention of leukocyte accumulation, the results also serve as a basis for studying important cellular and molecular events that contribute to tissue damage.

PMID: 8929502 [PubMed - indexed for MEDLINE]

About Entrez
Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI

Related Resources
Order Documents
NLM Mobile
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Note: Performing your original search, ***heparin "cell adhesion" stent***, in PubMed will retrieve ***6*** citations.

Display Abstract Show 20 Sort by Send to
All: 1 Review: 0

☐ **1:** Clin Cardiol. 2001 Feb;24(2):159-64. Related Articles, Links

Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation.

Atalar E, **Haznedaroglu I**, **Aytemir K**, **Aksoyek S**, **Ovunc K**, **Oto A**, **Ozmen F**.

Hacettepe University Faculty of Medicine, Department of Cardiology, Ankara, Turkey.

BACKGROUND: Adhesion molecules are known to be important in the regulation of endothelial cell and platelet functions. Increased platelets P-selectin expression is a marker of stent thrombosis after uncoated stent placement. HYPOTHESIS: The aim of this study was to compare the effects of intracoronary placement of phosphorylcholine (PC)-coated, versus heparin-coated, versus uncoated stents on platelets and endothelial activity. METHODS: Thirty patients (age 55 +/- 10, 27 men) with significant proximal left anterior descending coronary artery stenoses were randomized to elective implantation of PC-coated, versus heparin-coated, versus uncoated stents. Following stent placement, intravenous heparin and aspirin plus ticlopidine were administered. Venous plasma soluble E-selectin, sP-selectin, and intercellular adhesion molecule-l levels were measured before the procedure and 24 and 48 h thereafter as markers of platelet and endothelial cell activation. Patients were excluded if they had a disease known to influence platelet and endothelial cell function. RESULTS: Plasma sP-selectin levels decreased significantly after implantation of PC- and heparin-coated stents ($p = 0.04$), but remained unchanged in patients randomized to uncoated stents. Plasma sE-selectin levels increased significantly after uncoated stent placement ($p = 0.04$) and remained unchanged after coated stent implantation. CONCLUSION: In patients treated with combined antiplatelet therapy, implantation of PC- and heparin-coated stents decreased platelet activity without activating endothelial cells, whereas placement of uncoated stents led to endothelial activation without changing platelet activity. These results suggest that PC-coated and heparin-coated stents may be advantageous in limiting thrombotic complications.

About Entrez
Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI

Related Resources
Order Documents
NLM Mobile
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: Cancer. 1999 Jan 15;85(2):257-72.

Related Articles, Links

Actions of heparin that may affect the malignant process.

Engelberg H.

California Arteriosclerosis Research Foundation, Beverly Hills 90210, USA.

BACKGROUND: Heparin has many actions that may affect the malignant process, especially metastasis. METHODS: The author conducted an extensive review of the available medical literature about heparin activity that may apply to important factors involved in the malignant process. RESULTS: Thrombin is generated by tumors, and the resultant fibrin formation impedes natural killer cell activity. Microthrombi arrest tumor cells in capillaries. Heparin prevents the formation of thrombin and neutralizes its activity. Angiogenesis has an important role in metastasis; heparin minimizes angiogenesis via the inhibition of vascular endothelial growth factor, tissue factor, and platelet activating factor. It decreases tumor cell adhesion to vascular endothelium as it inhibits selectin and chemokine actions, and it also decreases the replication and activity of some oncogenic viruses. Matrix metalloproteinases, serine proteases, and heparanases have an important role in metastasis. Heparin decreases their activation and limits their effects. It competitively inhibits tumor cell attachment to heparan sulfate proteoglycans. It blocks the oncogenic action of ornithine decarboxylase and enhances the antineoplastic effect of transforming growth factor-beta. Heparin inhibits activator protein-1, which is the nuclear target of many oncogenic signal transduction pathways, and it potently inhibits casein kinase II, which has carcinogenic activity. Platelet-derived growth factor, which has oncogenic effects, is also inhibited by heparin, as are reverse transcriptase, telomerase, and topoisomerase prooncogenic actions. CONCLUSIONS: These various heparin actions justify clinical investigation of its possible beneficial effect on malignant disease.

Publication Types:
- Review

PMID: 10023691 [PubMed - indexed for MEDLINE]

(*Arteriosclerosis, Thrombosis, and Vascular Biology.* 1996;16:1312-1318.)

Articles

Monocyte Recruitment and Neointimal Hyperplasia in Rabbits

Coupled Inhibitory Effects of Heparin

Campbell Rogers; Frederick G.P. Welt; Morris J. Karnovsky; Elazer R. Edelman

the Departments of Medicine (Cardiovascular Division, Brigham and Women's Hospital) (C.R., F.G.P.W., E.R.E.) and Pathology (M.J.K.), Harvard Medical School, Boston, and the Harvard-MIT Division of Health Sciences and Technology (C.R., E.R.E.), Massachusetts Institute of Technology, Cambridge, Mass.

Correspondence to Campbell Rogers, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail cdrogers@bics.bwh.harvard.edu.

Among the many effects of heparin independent of its effects on coagulation are inhibition of vascular smooth muscle cell proliferation and regulation of leukocyte–blood vessel interactions. The potential link between these effects was examined in an animal model of vascular injury rich in inflammatory cells: the placement of endovascular metal stents in rabbit iliac arteries. Monocyte adhesion stimulated by early focal thrombus was maximal after 3 days, with infiltrating monocytes and intimal cell proliferation maximal after 7 days. Tissue monocyte number dictated cell proliferation at each time point (R^2=.92, P<.0001). Heparin reduced both early monocyte adhesion as well as monocyte infiltration within the neointima 7 and 14 days after stent placement. Reductions in adherent and tissue monocytes were commensurate with reductions in intimal cell proliferation and intimal thickening. At 14 days, heparin's inhibition of mononuclear cell adhesion was correlated with its suppression of intimal thickening (R^2=.82, P<.0001). Monocytes have been hypothesized to serve as markers, initiators, and promoters of arterial occlusive diseases. Heparin's ability to inhibit mononuclear cell adhesion and penetration and reduce neointimal size and cell proliferation after vascular injury may further implicate monocytes in the pathogenesis of neointimal

hyperplasia after mechanical arterial injury.

Key Words: heparin • monocytes • stent • restenosis